## REMARKS

By the present communication, Claims 1, 2, 11, 21, 37, 39, and 51 are amended, and Claims 56-58 are added. Claims 6, 8, 10, 13, 16, 18-19, 28, 32-35 are withdrawn from consideration. No new matter is presented. Support for the claim amendments can be found throughout the application as filed, including original Claim 2; p. 7, line 15; p. 8, lines 23-24; and p. 55, line 19.

A listing of previously presented claims readable upon the elected species was provided in the Amendment and Response dated 8/27/2007. New claims 56-58 read on the elected invention (Group I: Methods of selecting a combination of therapeutic agents) and also read upon the elected species of laser capture microdissection (from claim 3-6), reverse phase protein microarray analysis (from claims 10-13), a normal cell (from claims 14-16), same subject (from claims 17-19), abnormal growth (from claim 21), post-translational modification (from claims 22-23), EGFR phosphorylation and non-voltage gated calcium ion channels (from claim 26), specific Cox-2 inhibitor and carboxyamidotriazol (from claims 30-35), and a growth factor pathway (from claim 38).

Upon entry of the present amendment, Claims 1-5, 7, 9, 11-12, 14-15, 17, 20-27, 29-31, 36-44, and 51-58 will be pending and under examination. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### I. Overview

The present invention relates to methods for personalized medicine. In some diseases, such as cancer, there is a high degree of heterogeneity in the cellular circuitry between individuals (*See* Specification, pp. 75-76). By identifying the specific protein signaling defects in diseased cells, therapies may be tailored to a particular patient. Thus, the inventive methods relate to measuring the state of the cellular "circuitry" of a diseased cell, comparing that to the state of the "circuitry" in a reference cell, and then choosing combination therapies that restore

the circuitry of the diseased cell to a more normal state. This may be accomplished by selecting therapeutic agents that target interconnected nodes of signaling pathways. For example, the inventors discovered that administering a low dose of at least two therapeutic agents that target interconnected nodes of a pathway, it is possible to enhance the therapeutic efficacy, reduce the cytotoxicity, and minimize the shunting of targets along the pathway, compared to administration of higher doses of a single therapeutic agent (*See* Specification, Example 1, pp. 29-30). The claimed methods are directed to selecting an effective treatment for a variety of pathological conditions that relate to aberrant protein signaling, such as cancer. As described below in further detail below, these methods are not taught or suggested by the prior art.

## II. Rejection Under 35 U.S.C. § 102

Claims 1, 2, 7, 14-15, 20-23, 36-39, and 41-42 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bishop et al (U.S. Patent No. 6,316,462, herein "Bishop"). Applicants respectfully traverse the rejection.

The Office appears to misapprehend the teachings to Bishop. The instant claims relate to measuring the activity state of signaling proteins in diseased cells and determining which signaling proteins may be aberrant by comparison to a reference cell, and then selecting a combination of therapeutic agents which attempt to restore the aberrant signaling proteins to a more normal state. Bishop does not teach this method. Bishop analyzes the effects of various therapeutic agents on an induced (i.e., known) defect in the Ras signaling pathway. However, the reference does not teach measuring signaling proteins in diseased and reference cells and selecting combinations of therapeutic agents based on the observed defects. For the following reasons, Applicants submit that Bishop fails to teach all elements of Claim 1 and claims depending therefrom.

### A. The Ras-transformed Rat2 cells are not "diseased" cells.

The PTO maintains that Bishop's use of Ras-transformed Rat1 and Rat2 fibroblasts is a teaching of diseased cells. The Office points to Nasser et al (2006 *Current Topics in Medicinal*

*Chemistry* 6: 1109-1115) as evidence that "Rho GTPases of the Ras superfamily are involved in multiple cell functions and have been implicated in the pathology of various human diseases and cancer" (Final Office Action, p. 4). Applicants acknowledge that Ras proteins may be implicated in disease. However, the fact that Ras proteins may be involved in disease does not mean that a Ras-transformed fibroblast is a "diseased cell," as that term is understood from the specification of the present application. The Office appears to construe the term "diseased cell" over-broadly. The specification defines a diseased cell as "a cell that is identifiable (for example histologically or immunologically) as being involved in a pathological condition of a tissue." (Specification, p. 8, lines 13-14, emphasis added). A Ras-transformed fibroblast is not associated with any *pathological condition in a tissue*, since these cells are transfected *in vitro*. As such, the meaning of diseased cell in the Office Action does not comport with either the meaning ascribed to the term by those of skill in the art and/or the definition of the term provided in the specification. Consequently, Bishop does not teach the "diseased cell" specified in Claim 1 and the reference therefore fails to teach all elements of the claim.

**B. Bishop does not teach measuring the activity states for a plurality of signaling proteins in diseased and reference cells.**

Claim 1 recites the steps of measuring the activity states for a plurality of signaling proteins in diseased and reference cells. Bishop lacks any teaching of measuring the activity states of a plurality of signaling proteins in both diseased and reference cells. The Office Action states that

> Bishop et al teach, particularly in figure 5 bars 5-8, and paragraph bridging columns 3 and 4, a comparison of caspase activation (apotoptic potential) in ras transformed Rat2 cells vs. parental (control) Rat2 cells. It is the examiner's position that the control Rat2 cells of Bishop et al constitute a "reference" cell and further the ras transformed Rat2 cells are "diseased"....
> (Final Office Action, p. 4).

Even if Ras transformed Rat2 cells are "diseased" (and Applicants deny this is the case) and control rat2 cells are "reference" cells, *Bishop only measured the activity of one protein in transformed and control cells—caspase*. This is not measuring a plurality of signaling proteins,

as recited in the instant claims. And, although Bishop presents data measuring the phosphorylation state of ERK1 and 2 in H-Ras transformed Rat 2 cells, no measurement of ERK1 and 2 phosphorylation was performed in untransformed cells (Fig. 6). Bishop does not measure the activity states for a plurality of signaling proteins in both diseased and reference cells. Consequently, Bishop fails to teach this element of Claim 1.

**C. Bishop does not teach determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from the reference cell.**

The Office asserts that "in measuring extracted caspase activity, Bishop et al discern the activity state of many downstream proteins such as FAK and PAK2, albeit indirectly." (Final Office Action, p. 5). Applicants respectfully submit that *indirectly* discerning the activity state of downstream proteins by only measuring caspase activity is not sufficient to teach the claimed step of "determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for corresponding signaling proteins from the reference cell." The claim requires a comparison of the activity states of proteins that were actually measured. Because proteins downstream of caspase, such as FAK and PAK2, were not measured by Bishop, this reference fails to expressly or inherently teach this element of Claim 1.

**D. Bishop does not teach selecting at least two therapeutic agents, wherein the agents reduce the difference in the activity state that was detected in the measuring steps of the claimed method.**

Bishop lacks any teaching of the step of "selecting at least two therapeutic agents, wherein the agents reduce the difference in the activity state that was detected." Bishop contains no teaching of a selection of therapeutic agents based on the measured difference in activity states between the diseased cell and the reference cell. A comparison of the caspase activity between untreated H-Ras transformed and untreated Rat2 cells (the alleged diseased and reference cells, respectively) shows no significant difference (compare bars 1 and 5 in FIG. 5).

Therefore, Bishop did not select a combination of therapeutic agents based on a difference in activity state that was detected between the diseased cell and the reference cell.

The Office directs Applicants' attention to Figure 6 of Bishop which apparently indicates that PD0998059 and SCH 66336 prevent phosphorylation of ERK1 and 2. Applicants respectfully submit that this figure has been misapprehended. Bishop makes no comparison between ERK1 and 2 in Ras transformed Rat2 cells versus the parental control Rat2 cells. Figure 6 only shows the phosphorylation status of ERK1 and 2 in H-ras transformed cells over time and does not provide any comparative data regarding the phosphorylation status in control cells. Because no difference in activity states for ERK1 and 2 was determined between the two cell lines, the step of selecting a combination of therapeutic agents which reduces this difference has not been performed by Bishop. Therefore, Bishop fails to teach this element of Claim 1.

### E. Conclusion

Bishop fails to teach at least four elements of the method of independent Claim 1. As stated in the MPEP, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference" (MPEP 2131, *quoting Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). The overall process is not anticipated because the Office has drawn from the prior art piecemeal without consideration of the interrelated steps of the claimed methods. Applicants respectfully request withdrawal of the rejection of Claim 1 and claims depending therefrom.

## III. Rejections Under 35 U.S.C. § 103

In the Office Action, the claims stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable by Bishop as the primary reference in combination with a number of other references (detailed below). Applicants submit that because the cited art and the claimed invention have been misapprehended, the combined references do not establish a *prima facie* case of obviousness. For the reasons described in Section II above, Bishop fails to teach the

following elements of Claim 1: (1) diseased cells, (2) measuring the activity states for a plurality of signaling proteins in diseased and reference cells, (3) determining whether the activity states measured for the signaling proteins are different between the diseased and reference cells, and (4) selecting at least two therapeutic agents to target signaling proteins for which a difference in activity state was detected between the diseased cell and the reference cell. All of the deficiencies in Bishop are not taught or suggested by the secondary references cited by the Office. Because the prior art references fail to teach or suggest all of the claim limitations, a *prima facie* case of obviousness has not been established. Applicants' reasons are set forth in further detail as follows.

**A. Bishop in view of Lubman**

In the Office Action, Claims 1, 2, 7, 11-12, 14-15, 20-23, 36-39, and 41-42 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bishop in view of Lubman et al (U.S. Patent Publication 2005/0230315, herein "Lubman"). Applicants respectfully traverse because the combination of references fail to teach or suggest all elements of the claims and certain teachings of Lubman relied on by the Office are not prior art to the instant application.

According to the Office, Bishop does not teach reverse phase microarray analysis (claim 11) or phosphoprotein specific antibodies (claim 12). The teachings lacking from Bishop are allegedly taught by Lubman (Office Action dated 12/5/2006, p. 13). Lubman was filed on March 30, 2005, and claims priority to January 13, 2003. In the Amendment and Response, dated August 27, 2007, Applicants noted that Lubman is not 102(e) prior art because there is no support for the subject matter in Lubman's priority document (U.S. Provisional Application, No. 60/439,625). According to the Office, support for antibodies to phosphoproteins can be found at p. 7, lines 29-30 of provisional application, which is set forth below:

> [T]he protein microarray is analyzed to detect antibody binding (e.g., to identify antibodies that differentially bind from the experimental sample to a different degree than those from a control sample.

It is respectfully submitted that this passage fails to teach antibodies that *specifically bind* to phosphorylated signaling proteins as recited in Claim 12. A description of phosphoprotein-specific antibodies was added to the specification of the continuation-in-part application filed after the priority date of the present application. Nevertheless, the PTO asserts that "an antibody raised against the non-phosphorylated portion of a protein would specifically bind (i.e. not other proteins) a particular phosphorylated signaling protein, such as set forth in claim 12, in addition to the same signaling protein in unphosphorylated form" (Office Action, p. 7). Applicants respectfully disagree. Claim 12 recites that analysis of phosphorylated signaling proteins uses antibodies that *specifically bind* to phosphorylated proteins. One of skill in the art would understand that analysis of phosphorylated proteins is only possible if the antibodies specifically bind to the phosphorylated form of the protein, but not the unphosphorylated form. This type of antibody is not taught or suggested in Lubman's provisional. Thus, the combination of Bishop and Lubman fails to teach all elements of claim 12. A *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of this ground of rejection.

**B. Bishop in view of Moller**

In the Office Action, Claims 1, 2, 7, 14-15, 20-23, 36-39, and 41-44 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bishop in view of Moller et al (U.S. Patent No. 6,262,044, herein "Moller"). Applicants respectfully traverse because the combination of references fails to teach or suggest all elements of the claims. The deficiencies of Bishop are not taught or suggested by Moller. Moller teaches protein phosphatase inhibitors, but does not teach selecting a combination of two or more agents to reduce a measured defect in a protein signaling pathway.

Furthermore, the Office admits that Bishop does not teach a decrease in the activity state (claim 43) or a decrease in phosphorylation (claim 44) (First Office Action, 12/5/2007, p. 15). It was asserted that "it would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to use phosphatase inhibitors of Moller et al in lieu of the Ras pathway inhibitors in the ERK assay of Bishop et al" (Final Office Action, p. 7, emphasis

in original). Applicants respectfully disagree with the Office's reasoning. One of skill in the art would not have a reason to make the combination because Bishop teaches away from the proposed substitution. The Ras pathway inhibitors described by Bishop are directed to blocking phosphorylation of ERK1/2, specifically in tumorigenic cancer cells, thus leading to apoptosis of those cells (col. 2, lines 48-52). As the Examiner correctly points out, a phosphatase inhibitor would have the opposite effect—i.e. *increasing* the amount of phosphorylated ERK because the action of the Ras pathway kinases would not be reversible *in vivo* (First Office Action, 12/5/2006, p. 15). Therefore, substituting Ras pathway inhibitors with protein phosphatase inhibitors would lead to enhanced activity of ERK1/2. This would not produce the desirable outcome of inducing cell death of tumorigenic cancer cells, and one of skill in the art would not make the proposed substitution. Applicants respectfully request withdrawal of this ground of rejection.

**C. Bishop in view of Bonner**

Claims 1, 2, 3, 5, 7, 9, 14-15, 17, 20-23, 36-39, and 41-42 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bishop in view of Bonner et al (U.S. Patent No. 6,251,516, herein "Bonner"). Applicants respectfully traverse because the combination of references fail to teach or suggest all elements of the claims.

The deficiencies of Bishop are not taught or suggested by Bonner. According to the Office, Bonner teaches isolation of cellular material using laser capture microdissection (column 19, second paragraph) and isolation of normal and tumor tissue from the same patient. However, Bonner does not teach selecting a combination of two or more agents, wherein the agents reduce the differences in measured activity states between diseased and reference cells. Thus, a *prima facie* case of obviousness has not been established.

Moreover, one of skill in the art would not be motivated to modify or combine the references in the way asserted by the PTO. As set forth in the first Office Action,

> It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to analyze normal and tumor tissue from the same patient using laser capture microdissection per Bonner for susceptibility to the Ras pathway inhibitors per Bishop et al.
>
> One of ordinary skill in the art would have been motivated to use the analysis technique concerning normal and tumor tissue from the same patient using laser capture microdissection per Bonner for determining susceptibility to the Ras Pathway inhibitors per Bishop et al. because of the speed and efficiency afforded by laser capture microdissection, as noted by Bonner in column 19, line 60. (Office Action, dated 12/5/2006, p. 9)

It is unclear what meant by "determining susceptibility to the Ras pathway inhibitors" in normal and tumor tissue. Assuming that the Examiner means that the effects of the inhibitors are tested on laser captured cells cultured *in vitro*, cells isolated according to the methods of Bonner would be unsuitable for this kind of analysis. Bonner does not describe laser capture dissection methods that isolate live cells. Bonner teaches that proteins, mRNA and DNA from laser captured cells may be analyzed (col. 1, lines 24-26), but makes no mention of live cells. Therefore, one of ordinary skill in the art would not have a reason to make the combination proposed by the Office. It is respectfully submitted that a *prima facie* case of obviousness has not been established. Applicants request withdrawal of this ground of rejection.

**D. Bishop in view of Bilodeau and Tortora**

Claims 1, 2, 7, 14-15, 20-23, 26, 27, 29-31, 36-39, and 41-42 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bishop in view of Bilodeau (U.S. Patent Application 2002/0137755, herein "Bilodeau") as evidenced by Tortora et al (*Clinical Cancer Research* 9:1566-1572, herein "Tortora"). Specifically, the Office contends the combination of Bishop and Bilodeau renders claims 26, 27, and 29-31 obvious.

As stated in the Office Action, "[I]t would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to add the EGFR inhibitor(s) plus CAI or a COX-2 inhibitor(s) per Bilodeau et al to the Ras pathway inhibitor(s) assay of Bishop et al" (First Office Action, 12/5/2006, p. 10). While Bilodeau discloses many compounds that target various pathways in a cell, there is no teaching or suggestion regarding the selection of

therapeutic agents, wherein the agents reduce the differences in measured activity states between diseased and reference cells. Therefore, the combination of references fails to teach all elements of the claims. Applicants request withdrawal of this ground of rejection.

Applicants also point out that Tortora is not prior art against the instant claims. Tortora was published in April 2003. The present application has a priority date of March 10, 2003. Therefore, Tortora is not prior art under either 102(a) or (b). As stated in the MPEP, only subject matter that is prior art under 35 U.S.C. § 102 can be used to support a rejection under section 103 (MPEP 2141.01(I)). The Office's use of post-filing date references shows that impermissible hindsight has been used to establish obviousness (*See* MPEP 2141.01(III)).

**E. Bishop in view of Bilodeau, Bonner, Tortora, and Moon**

Claim 40 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bishop in view of Bilodeau and Bonner as evidenced by Tortora and Moon (U.S. Patent Application 2005/0282849, herein "Moon"). According to the PTO, Tortora teach that COX-2 is involved in the prostaglandin pathway, and a COX-2 inhibitor represents a prostaglandin pathway effector, as set forth in claim 30. Moon teaches that COX-2 inhibitors, CAI and tyrosine kinase inhibitors are useful agents in treating cancer.

The Office admits that Bishop in view of Bilodeau do not teach repeating the steps of claim 1 for a second diseased cell, as set forth in claim 40, but that

> [O]ne of ordinary skill in the art would have been motivated to ... repeat the steps of claim 1 with multiple [*sic*] samples comparing normal vs. tumor cells of Bonner et all in an effort to provide sufficient material for statistically meaningful analysis, as noted by Bonner et al in col. 11, line 63. (First Office Action, 12/5/2006, p. 12).

Applicants respectfully submit that claim 40 has been misapprehended. The "second diseased cell" is not simply a replicate of the first cell—it is obtained from a subject or a cell culture during or following administration of the combination of therapeutic agents to the subject or cell culture. Therefore, measuring the activity states for a plurality of signaling proteins in a

second diseased cell does not provide a means for statistical analysis. Neither Bishop nor Bilodeau teach measuring a second diseased cell having the characteristics of being isolated from a subject or cell culture following administration of the combination of therapeutic agents. Applicants request withdrawal of this ground of rejection.

As stated above, Tortora is not prior art against the instant claims. Likewise, Moon is not prior art against the instant claims. Moon was published on December 22, 2005, filed on April 18, 2005, and claims priority to a provisional application (60/552,725), filed March 15, 2004, all of which is after the priority date of the present application. Therefore, neither Tortora nor Moon are prior art under 102(a), (b), or (e).

**F. Bishop in view of Jain**

Claims 1, 2, 7, 14, 15, 20-23,25 36-39, 41, and 42 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Bishop in view of Jain (2000 *IEEE Transactions on Pattern Analysis and Machine Intelligence* 22: 4-37). Jain does not make up for the deficiencies of the primary reference. Jain is relied upon for teaching pattern recognition, as in claim 25, but contains no teaching or suggestion of measuring the activity states of a plurality of signaling proteins in diseased and reference cells and selecting a combination of therapeutic agents which reduces a detected difference between these cells. As such, the combination of references fails to teach or suggest all elements of the instant claims.

Moreover, the PTO has not provided a satisfactory reason for combining or modifying the references. The Office states, "One of ordinary skill in the art would have been motivated to use pattern recognition per Jain et al in analyzing the assays concerning Ras pathway inhibitors(s) of Bishop because pattern recognition is the best possible way of utilizing sensors (such as protein microarrays), as noted by Jain on page 4." (First Office Action, 12/5/2005, p. 14-15). First, neither Bishop nor Jain teach protein microarrays. Second, it is not clear how pattern recognition could be applied to the assays described in Bishop. Bishop only compared the activity state of one protein (caspase) in Ras-transformed versus untransformed fibroblasts. One of skill in the

art would understand that pattern recognition analysis is not applicable to the measured activity of a single protein—it is used to make comparisons between the activity states of many proteins, *e.g.*, entire pathways. As described in the specification,

> The similarity between the signaling derangements (as manifested in patterns of activity states for signaling proteins of one or more signaling pathways or networks) amongst multiple subjects having similar diseases may be detected and measured using pattern recognition methods such as statistical and neural network methods (see, for example, Jain et al., "Statistical Pattern Recognition: A review," IEEE Transactions on Pattern Analysis and Machine Intelligence, 22: 4-37, 2000). Pattern recognition may also be used to detect the similarity of a particular subject's signaling derangements to those seen in the diseases of others. Such comparisons may be useful for selecting an appropriate treatment for the subject (that is, a treatment based on success in other subjects with similar derangements).... These techniques are also helpful for comparing diseased cells to normal cells for the purpose of identifying deranged signaling pathways.
> (Specification, p. 16, lines 11-25).

According to the MPEP, "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the reference are not sufficient to render the claims *prima facie* obvious. *In re Ratti,* 270 F.2d 810, 123 USPQ 349 (CCPA 1959)." (MPEP 2143.02(VI)). For the reasons described above, pattern recognition is not operable in the context of the assays described in Bishop. Applicants request withdrawal of this ground of rejection.

### G. Paweletz in view of Bishop

In the Office Action, Claims 51-55 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Pawletz et al (2001 *Oncogene* 20:1981-1989) in view of Bishop. Applicants respectfully traverse the rejection.

The Office admits that Paweletz does not teach selecting a combination of at least two different therapeutic agents that target two or more different members of a protein signaling pathway or network comprising an individual signaling protein for which a difference in activity state between was detected between the diseased cell and the reference cell, wherein the agents reduce the difference in the activity state that was detected. As described in Section II above,

Bishop also does not teach this element of the instant claims. Bishop did not select a combination of therapeutic agents based on a difference in activity state was measured and detected between the diseased cell and the reference cell. Bishop only teaches administration of a farnesyl protein transferase inhibitor and an additional Ras signaling pathway inhibitor for the treatment of cancer. Bishop does not indicate that the selection of these therapeutic agents is based on any assessment of the state of the Ras signaling pathway in diseased and reference cells.

Therefore, the combination of references fails to teach or suggest all elements of the claims. A *prima facie* case of obviousness has not been established. Applicants respectfully request withdrawal of this ground of rejection.

## IV. Rejection Under 35 U.S.C. § 112, Second Paragraph

In the Office Action, claims 3-5, 11-12 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claim 3 was rejected for alleged lack of antecedent basis for the phrase "the subject." An apparent typographical error in the Amendment and Response dated August 27, 2007, changed the first instance "a subject" in Claim 3 to "the subject." No amendment to Claim 3 was intended. In response, Applicants have corrected the typographical error. The status identifier for this claim has been left as "original" because the text of the claims has not been amended and is identical to originally-filed claim 3. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 11 was rejected for alleged lack of antecedent basis for the phrase "wherein measuring the activity states of the plurality of signaling proteins." In response, Applicants have amended the claim to recite that the step of measuring refers to proteins extracted from the diseased cell and the reference cell. As such, the rejection is now moot. Applicants request withdrawal of this ground of rejection.

## V. Information Disclosure Statement

In the Office Action, the Information Disclosure Statement was objected to because the relevant pages, date, and place of publication were missing from citations 17-18, 64, and 132 of

the non-patent documents. Web addresses and last access dates have been provided for citations 17-18 in the Supplemental IDS filed herewith. Likewise, the publication source and date for citation 64 (Igarashi et al., "Development of a Cell Signaling Networks Database" 1997, *Pac Symp Biocomput,* 187-97) is listed in the supplemental IDS filed herewith. Applicants request that this objection be withdrawn and citations 17, 18, and 64 be considered and listed on this issued patent. Citation 132 is an unpublished manuscript inadvertently listed on the IDS. The submission of this document is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR § 1.56(b). The manuscript was published as Winters et al., "Supra-additive growth inhibition by a celecoxib analogue and carboxyamido-triazole is primarily mediated through apoptosis," *Cancer Res* 65(90); 3853-3860 (May 1, 2005).

Applicants direct the Examiner's attention to citations 56, 112, 114, 115, and 119 of the Information Disclosure Statement, which have not been initialed in either the 12/5/2006 or 11/15/2007 Office Actions. Applicants respectfully request that the citations be considered (insofar as the abstract) and listed on the issued patent.

## VI. Withdrawn Rejections

Applicants acknowledge that the Examiner has withdrawn the rejections under 35 U.S.C. § 112, second paragraph , regarding the terms "deranged cell signaling pathways," "selected" and "prior success," and the provisional rejection of claims 1 and 25 on the ground of nonstatutory obviousness-type double patenting as unpatentable over copending Application No. 11/189,808 in view of Bishop and Jain.

## VII. Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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